

March 14, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20857

Re: Docket Number 2006N-0062; Expanded Access to Investigational Drugs for Treatment Use; 71 Federal Register 75147; December 14, 2006

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to provide the following comments on the above cited proposed rule. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated \$39.4 billion in 2005 in discovering and developing new medicines. Industry-wide research and investment reached a record \$51.3 billion in 2005.

General Comments

1. Page 75149, Section II - The preamble states that "...describing, in detail, in the proposed rule the criteria, submission requirements, and safeguards for the different types of expanded access...the agency seeks to increase awareness and knowledge of expanded access programs...." This, "...should make investigational drugs more widely available in appropriate situations." It goes on to say that "...clearly articulated procedures for obtaining investigational drugs for treatment use should ease the administrative burdens...."

Comment: Except for regulated industry, healthcare providers in academic medical centers, and regulators, the Code of Federal Regulations is not widely accessed by providers of healthcare. As a tool to increase knowledge of expanded access, rewriting regulations may be the least effective vehicle available to the Agency.

Recommendation: Guidance and a widely distributed, well-targeted educational program would be far more effective than rewriting the regulations as a tool to inform the public about access to investigational drugs for "treatment" use. The FDA may wish to consider utilizing sponsors with intermediate and larger size expanded access programs themselves for communication of appropriate and non-promotional information about the existence of the applicable expanded access program.

Pharmaceutical Research and Manufacturers of America

2. Page 75154, Section III G, “Expanded Access for Intermediate-Size Patient Populations (Proposed §312.315)” – Column 2

The preamble states that this provision is also intended “...to allow uninterrupted therapy when an approved drug is not being manufactured in a manner consistent with the specifications on which the approval is based (good manufacturing practice (GMP) violations) and therefore cannot be marketed under the new drug applications (NDA).”

The preamble also states that this provision “...could also be used in a drug shortage situation to make available an unapproved drug containing the same active moiety as the approved drug that is in short supply (e.g., a drug product approved in another country).” In addition, one of the criteria that would apply to intermediate-size patient populations is sufficient evidence that “the drug” is safe...for the approximate number of patients expected to receive the drug.

Recommendations: (i) The populations seeking uninterrupted therapy in the situations cited may be large and, therefore, providing products in these situations would seem to fall more appropriately under proposed §312.320. (ii) Not all shortages in which uninterrupted therapy is important will involve patients with conditions that meet the criteria for expanded access programs as described in proposed §312.300 (“*The aim of this subpart is to facilitate the availability to investigational new drugs to seriously ill patients....*”). Therefore, we recommend including a definition of “expanded access” which incorporates both the concept of facilitating availability of investigational new drugs to seriously ill patients to diagnose, monitor, or treat a patient’s disease or condition when there is no comparable or satisfactory alternative therapy, and the concept of allowing uninterrupted therapy in cases of shortage of approved products for the reasons cited above.

3. § 312.8(c) and § 312.8(d)(3) – Charging for unapproved drugs in expanded access programs – We recognize that there may be extraordinary circumstances in which the ability of a sponsor to charge may make certain unapproved drugs more readily available to patients who lack alternatives. The proposed rule, “Charging for Investigational Drugs” (71 FR 75168, December 14, 2006), however, would require FDA to review information submitted to demonstrate that the calculation for cost recovery is consistent with the allowable direct and indirect costs identified in proposed § 312.8(d)(1)(i) and (ii). Such determinations are outside of FDA’s expertise.

Recommendation: If such an arrangement is deemed to be in the public interest, we recommend consideration of allowing sponsors to charge a reasonable administrative fee rather than basing such charges on a FDA reviewed calculation of direct costs. Such a fee could be set by the sponsor after consulting with patient groups or based on the cost of treatment with other drugs in the class or other therapies. This would simplify the process while encouraging sponsorship of expanded access programs.

Specific Comments

4. § 312.42 and Page 75150 – Clinical holds – The proposed rule describes clinical hold criteria for expanded access programs. They are: (1) “the pertinent criteria in subpart I”

are not satisfied, or (2) if the protocol or IND does not comply with the requirements of subpart I.

Comment: While the “requirements” of subpart I include the administrative details related to a complete submission, the “criteria” include the requirement for potential benefit to the patient to justify the potential risks of treatment. Therefore, it becomes extremely important to assure a high degree of clarity about the reasons for a clinical hold on an expanded access IND or protocol to assure that other studies of the drug are not unintentionally affected by the action. Lack of clarity on the issues leading to the clinical hold of an expanded access protocol could close down an entire development program.

Recommendation: Language in the final rule on clinical holds for expanded access programs should clearly require FDA to cite the specific reasons for a clinical hold on an expanded access program. The Agency should apply the same level of rigor to evaluation of an expanded access program for clinical hold as it does for clinical development programs. We also recommend addressing a legitimate way to supply patients who, regardless of clinical hold on the expanded access program, were clearly benefiting from the therapy.

5. § 312.300(a) **General** – *Scope* “The aim of this subpart is to facilitate the availability of investigational new drugs to seriously ill patients when there is no comparable or satisfactory alternative...” And

§ 312.305(a) **Requirements for all expanded access uses** – *Criteria* “FDA must determine that (1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition...”

Comment: There is a difference between being seriously ill and having a serious condition. Most progressive diseases for which there is no satisfactory therapy to interrupt the course of the disease are “serious conditions.” Patients in the early stages of such diseases may not be seriously ill, however.

The proposed regulation, like the current treatment use regulation at § 312.34, specifies not just “life-threatening” but “immediately life-threatening” in the criteria [§ 312.305(a)(1)], and the current definition of that term is retained in § 312.300(b). Subpart E of Part 312, on the other hand, deals with drugs intended to treat “life-threatening” [not “immediately life-threatening”] and severely debilitating [not “serious”] illnesses and, for the purposes of that part, the term “life-threatening” is defined. Subpart E, however, also includes a section on treatment protocols (§ 312.83), which refers to current § 312.34 and 35.

Revision of the rule governing expanded access provides an opportunity to clear up some of the confusion associated with the use of similar but different terms in current regulations. We do not believe these regulations are intended to apply to significantly different populations but, rather, different terminology has been used at different times in the evolution of regulations governing development of drugs for serious conditions. There appears to be a continuum from “serious disease or condition” to “seriously ill

patients” to “life-threatening disease” and, finally, “immediately life-threatening disease.”

Recommendations:

1) We believe that the revised expanded access regulation should apply to patients with serious diseases or conditions who are at any stage of this continuum for which there is no satisfactory available therapy.

2) In addition, we recommend consideration be given to deleting “immediately life-threatening” from the expanded access rule and incorporating into the regulation the discussion of “serious” from the July, 2004 “Guidance for Industry – Fast Track Drug Development Programs – Designation, Development, and Application Review.” This discussion states:

*...determination of the seriousness of a condition:
... is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes [such as] ... inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses, and many other diseases.*

For a condition to be serious, the condition should be associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient but the morbidity need not be irreversible, providing it is persistent or recurrent.

This excellent statement on the determination of seriousness of a condition would significantly clarify the applicability of expanded access. In addition, because any condition that is life-threatening or immediately life-threatening is also serious, there would be no need to define terms describing stages of disease further down the continuum.

6. § 312.305(c)(2) – “An individual or entity that submits an expanded access IND or protocol under this subpart is considered a sponsor....”

Recommendation: We recommend using the term “person” instead of “individual or entity.” “Person” is defined in the FD&C Act [§ 201(e)] and includes “individual, partnership, corporation, and association.”

7. § 312.305(c)(5) – “In all cases of expanded access, sponsors are responsible for...providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (e.g., providing the investigator's brochure, if there is one)...”

Recommendation: With respect to an investigator's brochure, rather than stating "if there is one," we recommend stating "if required under § 312.55 (Informing investigators)."

8. Pages 75151 and 75166: *"Under proposed § 312.305(a)(3), FDA must determine that providing the investigational drug for the requested use will not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the development of the expanded access use. Section 561(b)(3) and (c)(5) of the act requires FDA to make this determination. The most effective way to make a drug available to those who can benefit from the drug is to market it. Therefore, it is important to ensure that expanded access use does not compromise enrolment in trials needed to demonstrate the safety and effectiveness of the drug."*

Recommendations:

1) To promote consistency across review divisions, we recommend including examples of factors that will generally be considered by the FDA in making this determination to further define the meaning of "interfere" with drug development.

2) Because a large expanded access program or an expanded access program for an uncommon condition could affect enrollment in clinical trials of all investigational products for the same use, we recommend that the effect of such programs on the development of products other than the one being considered for expanded access be included as a criterion for FDA to consider when authorizing such programs.

9. § 312.310(a)(2) – *"FDA must determine that the patient cannot obtain the drug under another type of IND or protocol."*

Recommendation: Delete the word "type" from the above statement.

10. § 312.310(c)(1) – *"Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy."*

Recommendation: The regulation should describe submission requirements and processes to extend the treatment use in those instances where the initial authorization was for a single course of therapy but additional courses are warranted (based, for example, on favorable response or the judgment of the physician that additional courses are appropriate).

11. Page 75151 - *"Third Criterion: Varying levels of evidence of safety and effectiveness with more required for the treatment of a large patient population. As the seriousness of the disease increases it may be appropriate to authorize expanded access use based on less data. For example to support treatment use for an individual patient with an immediately life-threatening condition that is not responsive to available therapy, ordinarily, completed phase I safety testing in humans at doses similar to those to be used in the treatment use, together with preliminary evidence suggesting possible*

effectiveness, would be sufficient to support such a use. In some cases, however, there may be no relevant clinical experience, and the case for the potential benefit may be based on pre-clinical data or on the mechanism of action."

Recommendation: There should be, at the very least, some preliminary clinical safety data available before expanded access (treatment use for an individual patient) is granted. (See comment #20.)

12. Footnote on Page 75151 – *"This proposed rule continues to describe the specific type of expanded access for treatment use that makes investigational drugs available to large populations as the "treatment IND" or "treatment protocol." We recognize that it may be confusing to carry over this terminology from our current regulations (§§ 312.34 and 312.35). However, this terminology has been used since 1987, and we believe it would be more confusing to change terminology when the nature of this type of treatment use remains essentially unchanged. The broader term "expanded access" refers to all kinds of treatment use. We solicit comment on this approach."*

Recommendation: We believe the terms "treatment IND" and "treatment protocol" as used in the existing regulations (21CFR § 312.34 and 21CFR § 312.35) are, by themselves, very confusing, despite their being in use for nearly 20 years. Moreover, since the individual patient and intermediate-size patient population expanded access for treatment use will each require submission of an IND or a protocol, we believe retaining the nomenclature will make it more confusing. We recommend that the Agency change the nomenclature to "large-size patient populations" as a new term for consistency with nomenclature for other types of expanded access treatment uses.

13. § 312.315(a)(3) and Page 75154 (preamble) – Proposed § 312.315(a)(3)(i) states, *"Expanded access under this section may be needed in the following situations...(i) (T)he drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application..."*

Recommendation: The final rule should reflect that the rules are permissive only and that sponsors/manufacturers are not obligated to sponsor, or continue to sponsor, any expanded access program.

14. § 312.315 – Intermediate-size patient populations

§ 312.315(b) and (c) – *"Criteria – The criteria in §312.305(a) must be met...." and "Submission – The expanded access submission must include information adequate to satisfy FDA that the criteria in §312.305(a)...of this section have been met."*

Comment: § 312.305(a) describes the criteria for FDA to determine whether expanded access is appropriate. These include (i) whether the disease is serious or immediately life-threatening with no satisfactory alternative therapy; (ii) that potential patient benefit outweighs the potential risk, and (iii) that expanded access will not interfere with progress towards marketing approval of the drug. If FDA makes a request for a sponsor to consolidate expanded access under the conditions in proposed § 312.315 because of

having received a significant number of individual requests, FDA should have already made the determination that the criteria in § 312.305(a) are met and, in fact, should certify in its request to that effect.

Recommendation: The final rule should specifically state that FDA will consider the nature of the disease, the risk-benefit to the population, and the impact on drug development and concluded that intermediate-size expanded access is appropriate before making a request to a sponsor for consolidation.

15. § 312.315(c)(2) – *“If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.”*

Comment: There are many reasons why a particular product may not be considered a viable development candidate, including internal competition for resources among product candidates in the development portfolio. Provided adequate information is submitted about the drug to allow FDA to make a risk-benefit decision on the use of the drug in an intermediate-size patient population, discussion of the reasons the drug is not being developed and speculation about conditions that might favor development are, at best, tangential to FDA’s regulatory and public health mission.

The implication that a sponsor’s agreement to consolidate expanded access requests into an intermediate-size population program also creates an obligation to justify to FDA the decision not to develop a commercial product may have a chilling effect on willingness to participate in such consolidation.

Recommendation: This provision should be eliminated.

16. § 312.315(d)(1) – *“Safeguards. Upon review of the IND annual report, FDA will determine whether it is appropriate for the expanded access to continue under this section.”*

Recommendation: This is the only reference in the proposed rule to discontinuation of an intermediate-size expanded access program. The final rule should contain a clearly articulated right of the sponsor to discontinue expanded access use under § 312.315.

17. § 312.315(d)(1)(i) – *“If the drug is not being actively developed or if the expanded access use is not being developed (but another use is being developed), FDA will consider whether it is possible to conduct a clinical study of the expanded access use.”*

Recommendation: This provision should be deleted. There is no discussion of the relevance of this determination in the preamble to the proposed rule. In the preamble, however, this provision is stated as “FDA will consider whether it is possible to conduct a clinical study to develop the expanded access use for marketing.” As we noted in comment #15 above, there are a number of reasons why a sponsor may conclude that product development for a certain use is not viable. In making such a determination, a sponsor will have considered whether it is possible to conduct a full development program and whether the product is a reasonable candidate for such a program.

Agreement to open an intermediate-size expanded access program should not impose a need to justify development decisions and priorities or suggest an obligation to develop a particular compound.

18. § 312.315(d)(1)(iii) – *“As the number of patients enrolled increases, FDA may ask the sponsor to submit an IND or protocol for the use under §312.320” and §312.320(b) – “Submission. The expanded access submission must include information adequate to satisfy FDA that the criteria in §312.305(a)...have been met.”*

Recommendation: (See comment #14) -- Before FDA makes a request for a sponsor to submit a treatment IND or protocol under § 312.320, FDA should determine that the criteria under § 312.305(a) have been met. The final rule should specifically state that FDA will not make such a request unless it has considered the nature of the disease, the risk-benefit to the population, and the impact on drug development, and concluded that a treatment IND or protocol is appropriate.

19. §§ 312.310(c)(4) & 312.315(d)(1)(iii) provide for FDA to ask a sponsor to submit an IND or protocol under the proposed provision for intermediate-size patient populations (§312.315) when individual patient requests reach a “significant number,” or under the treatment IND or treatment protocol provision (§312.320) as the number of patients enrolled under §312.315 increases.

Recommendation: As in our comments to #13 above, the final rule should reflect that the rules are permissive only and that sponsors/manufacturers are not obligated to sponsor, or continue to sponsor, any expanded access program.

20. § 312.320 Page 75168 - Expanded Access Treatment IND or Treatment Protocol-

Recommendation: We recommend including reference to mechanisms to ensure equitable access when supplies and resources are limited and expanded access programs extend to potentially large populations.

21. At the conclusion of treatment, the licensed physician or sponsor (whoever made the expanded access submission) must provide a written summary of the results of the treatment use, including unexpected adverse drug experiences.

Recommendation: Presumably, this mandatory written summary will be submitted to the FDA but it is not clear as written. We think that it would be appropriate for the agency to clarify to whom the written summary will be submitted to.

22. Page 75155 “Open-label Safety Studies” – *“FDA is concerned that sponsors have used programs other than treatment INDs or treatment protocols to make investigational drugs available to large populations for treatment use, particularly by identifying such programs as “open-label safety studies.” And, “Consequently, in the future, the agency intends to evaluate whether proposals for open-label safety studies should be treatment INDs or treatment protocols that would have to meet the criteria in proposed § 312.320. A study described as an open-label safety study that provides broad access to an*

investigational drug in the later stages of development, but lacks planned, systematic data collection and a design appropriate to evaluation of a safety issue is likely to be considered a treatment IND or treatment protocol."

Recommendation: This passage suggests that FDA would review all open-label safety studies to determine whether a treatment IND or treatment protocol would be the more appropriate procedure. If so, presumably, the sponsor would be asked to resubmit the protocol as a treatment protocol or treatment IND which the Agency would re-review upon receipt. The benefit of this approach is unclear. The preamble states that treatment INDs or protocols are more appropriate under these conditions because they undergo a more formal review process that would consider the impact of expanded access on enrollment and progress of development. From a public health standpoint, including patient access, patient protection, and appropriate use of scarce resources, the value of this approach is not justifiable. We recommend that this concept not be carried forward into the final rule.

Sincerely,

A handwritten signature in cursive script, appearing to read "Alan Goldhammer".